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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,667	11/14/2001	Avi J. Ashkenazi	P2730P1C4	3324

35489 7590 01/04/2005

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,667	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The rejections of claims under 35 USC 112, second paragraph and first paragraph-written description, are withdrawn in view of the amendment to the claims and Applicant's argument or moot in view of cancellation of the claim.

Rejections of cancelled claim 124 are moot.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

The Declarations of Drs. Ashkenzi and Polarkis under 37 CFR 1.132 filed 10/20/04 is insufficient to overcome the rejection of claims 119-123 based upon 35 USC 101/112, first paragraph, as set forth in the last Office action because: they are not sufficient to overcome the rejections for the reasons discussed in response under the rejections below. While the Declaration of Ashkenazi shows that "real-time PCR" is a reliable means of determining gene copy number in cells or tissues, there are utility and enablement issues of protein *vs.* DNA not resolved by the declaration that require the rejection to be maintained. While statements are made in the Polarkis Declaration about correspondence of DNA amplification and encoded polypeptide increase in particular cell types based on antibody binding studies, there is evidence on the record to refute the generalization of correspondence and there is no evidence accompanying the declaration to support the correspondence for PRO 290. The utility and enablement for the claims are further discussed under the appropriate section for the rejections below.

Claim Rejections - 35 USC § 101/112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action.

Claims 119-123 remain also rejected under 35 U.S.C. 1 12, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for the reasons set forth in the previous Office action.

Applicant argues that gene amplification, which is well described in the specification, is a patentable utility for the PRO290 protein and by extension the antibody which binds the portein. The argument has been fully considered, but is not persuasive. As stated in the previous Office action (p. 3, lines 9-18):

Even though the nucleic acid has utility as a probe for screening for lung tumor cells, the encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in lung tumor versus normal tissue. Even if the DNA has utility as a lung tumor marker, the encoded protein does not have utility because it is not known what the protein does or if the level of PRO290 protein in lung tumors corresponds to nucleic acid transcript level, i.e., if an increased gene amplification in lung tumors corresponds to an increased amount of expressed protein. If the antigen does not have utility, the antibody that binds that antigen likewise does not have utility. It does not necessary follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development.

Gene amplification alone does not provide utility for an encoded polypeptide without a further showing of a reasonable expectation that the polypeptide itself has an significantly elevated or decreased level associated with a tumor, disease, *etc.*

Applicant argues that the data of Pennica et al. about the correlation or lack thereof between gene amplification and WISP protein expression is not generalizable. The argument has been fully considered, but is not persuasive. While Pennica et al. alone does not support a lack of correlation, the references relied upon together do. Pennica et al. show an example of the unpredictability correlating gene amplification and protein level. Haynes et al. found a "general trend" but no significant correlation between nucleic acid level and translation. It is maintained that the correlation between each gene and corresponding protein in tumors is unpredictable, and Applicants have presented no showing that would allow the skilled artisan to conclude that it is more likely than not that the amount of *both* the PRO290 encoding gene and protein are increased in squamous cell-type lung carcinomas (SqCCa).

Applicants argue that the Haynes et al. publication does not support the rejection. Applicants characterize Haynes et al. as teaching there is a general trend but no strong correlation between polypeptide expression level and transcript level. Applicants criticize Haynes et al. for being directed to a study of yeast polypeptides. Applicants further characterize Haynes et al.'s conclusions as showing that there is a positive correlation between transcript and polypeptide for most of the 80 yeast polypeptides studied, but the correlation is not linear and thus one cannot accurately predict polypeptide levels from mRNA levels. Applicants stress that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and polypeptide. Applicants conclude that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO290. There is no evidence regarding whether or not the PRO290 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Since the instant claims are directed to and PRO290 **antibodies**, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Additionally, Konopka et al. (PNAS, 83:4049-52. 1986) states that, "Protein expression is not related to amplification of the *abl* genenbut to variation in the level of bcr-abl mRNA production from a single Ph1 template" (see abstract). Konopka et al. also provide evidence showing lack of correlation between gene amplification and increased polypeptide levels. Haynes et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO290 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. One skilled in the art would do further research to determine whether or not the PRO290 polypeptide levels increased significantly in

the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, *i.e.*, it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicants' claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicants refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al., pp. 10-12) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicants characterize Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicants characterize Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicants characterize Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. The arguments relating to these references have been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO290 in the instant specification. That is, it is not clear whether or not PRO290 is in a gene cluster in a region of a chromosome that is highly

amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the later three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO290 polypeptides and cognate antibodies have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicants' arguments (pp. 11-12) directed to the Polakis declaration filed under 37 CFR 1.132 have been fully considered but are not found to be persuasive for the following reasons. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant

specification provides no information regarding increased mRNA levels of PRO290 in tumor samples relevant to normal samples. Only gene amplification data was presented. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argue (p. 12) the declaration filed by Dr. Ashkenazi under 35 USC 1.132 supports the gene amplification data in the present application because "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product," that in itself provides important information for cancer diagnosis and treatment. There is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification.

Applicants argue (p. 13) that the teachings of Hanna et al. show that for Her-2, to diagnose breast cancer both gene product presence as well as amplification of the gene itself provides the most complete information. The argument has been fully considered, but is not persuasive. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that, "In general, FISH [gene] and IHC[protein] results correlate

well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, the issues of Her-2 cannot be generalized to any gene expressed in a tumor.

The arguments for the rejection under 35 USC 112, first paragraph, were presented with those of the rejection under 35 USC 101 and also answered above.

For all of these reasons, the rejections are maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
December 14, 2004

LORRAINE SPECTOR
PRIMARY EXAMINER